REGIONAL CEREBRAL IMPEDANCE CHANGES IN ALERTING, ORIENTING AND DISCRIMINATIVE RESPONSES; THE ROLE OF NEURONAL ELEMENTS IN THESE PHENOMENA

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Condensed Title: Regional Impedance and Behavior

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Abstract

Electrical impedance was measured in the hippocampus, amygdala and midbrain reticular formation during alerting, orienting and discriminative performances in the cat. Measurements were made in focal volumes of approximately 1·0 cmm at 1000 cycles per second with coaxial electrodes. In the fully trained animal, computed averages of hippocampal impedance decreased by as much as 8 per cent of baseline during visual discrimination, whereas alerting and orienting responses immediately preceeding were not accompanied by comparable impedance changes. Similar measurements in the rostral midbrain reticular formation showed small responses during orientation and discrimination, and less constantly during alerting responses. The amygdala exhibited consistent responses only in the alerting epoch. The magnitude of the responses in hippocampus and midbrain increased with the level of behavioral performance. When behavioral cues were reversed, the hippocampal impedance response sharply increased on the first post-reversal day, but rapidly declined thereafter and disappeared. Further retraining was associated with gradual reappearance of the response. Similar relationships to levels of performance, and to cue reversal with retraining, were noted in midbrain responses, but without an enhancement immediately after cue reversal. Variability of impedance was calculated in early, mid and late training, and after cue reversal and during retraining, for the consecutive epochs of alerting, orienting and discriminative behavior. In hippocampus and midbrain, variability declined progressively for the whole test epoch at increasing performance levels, but increased sharply immediately after cue reversal, declining again with retraining. Amygdaloid variability was lowest immediately after cue reversal. Unilateral visual

cortical resection, leading to retrograde loss of about 80 per cent of lateral geniculate neurons, was followed by perturbations in geniculate impedance baseline from 10 to 30 days postoperatively. Subsequently, responses to a cyclohexamine drug were reduced in the degenerated nucleus to about 20 per cent of those in the intact nucleus. In modeling these impedance phenomena of regional specificity and apparent dependence on intact neuronal populations, it is proposed that significant current pathways may involve both neuroglial elements and an intercellular substance containing appreciable quantities of mucoproteins and mucopolysaccharides. Possible modulation of conductivity in this substance by adjacent neuronal and neuroglial elements is reviewed, in terms of information transaction and storage in a micrometabolic module of neurons, neuroglia and intercellular fluid.

Introduction

Correlation of essential elements of behavior, including arousal, orienting and learned discriminative habits, with electrophysiological phenomena recorded in cortical and subcortical nuclei, has added much new knowledge of cerebral system organization (3, 13, 19, 29, 35). It has also opened windows on intimate aspects of neuronal firing patterns in the course of these responses (22, 28, 32). Yet these unit discharges have remained of baffling complexity, and analysis of EEG and intracellular wave patterns elicited in the same context has indicated that they may only indirectly reflect long-term changes in tissue states associated with the storage of information.

Nor has it been clear that storage of information occurs exclusively in the neuronal compartment of cerebral tissue (18). Intimate envelopes of mucopolysaccharide and mucoprotein around the neuron, and intervention of a substantial neuroglial compartment between neuronal and vascular elements, have emphasized the metabolic interdependence of neurons and glial cells. In previous studies, measurements of electrical impedance in focal volumes of cerebral tissue were used to detect changes in tissue states associated with sleep and wakefulness, and also in relation to orienting and discriminative behavior (1, 2). The probable pathways for low-level impedance measuring currents used in these earlier studies were through extracellular fluid and neuroglial cells, since both may be assumed to offer current pathways preferred over the substantially higher impedance route through neuronal membranes.

Impedance shifts of the order of 15 per cent of baseline values occurred during a learned performance. Their magnitude lends support to

the view that they also occur in non-neuronal structures, although they may arise through neuronal influences on these adjacent elements. The basis of the regional qualitative differences described here thus appears to lie in the local characteristics of non-neuronal elements. The present study has involved examination of regional characteristics of these impedance responses in relation to different levels of learning, and following cue reversal with retraining; it has also included studies of the effects on drug-induced impedance responses of loss of neuronal elements in cerebral nuclei.

Material and Methods

A. Behavioral studies

In the behavioral studies, seven cats were prepared with chronically implanted electrodes, in bilaterally symmetrical placements in the dorsal hippocampus, amygdala and midbrain reticular formation. Electrode placements were subsequently checked histologically and, in the hippocampal placements, were found to lie in the pyramidal cell layer, or more medially amongst cellular elements of the subiculum; in the rostral midbrain reticular formation, they were in the dorsal tegmentum adjacent to the periaqueductal gray matter; and in the amygdala, in basal or lateral nuclei.

Impedance measurements were made at 1000 cycles per second, using a Wheatstone bridge technique, in which the coaxial impedance measuring electrode, with a small volume of conducting brain tissue surrounding its tip, formed one leg of the bridge (1, 20, 21). Electrode placements have been checked routinely by histological examination of frozen sections.

The test animals were deprived of food, but not water, for 23 hours prior to each training session. Behavioral training involved an automated

test procedure in a modified T-maze, with successive presentation of alerting, orienting and discriminative epochs. An alerting stimulus (a 500 cycles per second tone lasting 0.5 second) was first presented. This was followed 1.6 seconds later by illumination of one goal area at the end of the T-box, as a cue for the subsequent light-dark discrimination. At this stage, the cat was able to orient towards the test situation through transparent doors in the start box. These doors opened 1.6 seconds later, and the approach to the food reward (milk, presented automatically upon correct choice) lasted about 1.5 seconds. Cues and photoelectrically generated signals relating to response latency were recorded together with impedance and EEG signals on a Sanborn 150 chart recorder.

Each day's training involved 30 trials. Averages of the impedance records for each test day were prepared on-line with a Mnemotron CAT computer, using an 8 second analysis epoch. In subsequent analyses with an IBM 7094 computer, variability between daily averages was calculated over epochs of 5 successive days, in the form of standard error of the mean trace, at chance levels of performance, and at 80 percent and close to 100 per cent performance. Variability was similarly calculated immediately after cue reversal, and in the course of retraining in the reversed paradigm.

B. Studies in degenerated cerebral tissue

In six cats, the visual cortex was unilaterally ablated about two months after bilateral implantation of two coaxial impedance electrodes in each lateral geniculate nucleus. One coaxial electrode was placed anteriorly in the geniculate nucleus, and primarily spanned optic tract fibers. The other was located posteriorly in the cellular laminae of the nucleus. Stable levels in daily impedance measurements in these electrodes

was attained 20 to 30 days after implantation. Changes occurring during retrograde degeneration will be discussed below. Histological evidence indicated about 80 per cent neuronal loss following cortical ablation and confirmed accuracy of electrode placements.

Pharmacological manipulation of impedance values in the normal and degenerated geniculate tissue was initiated not less than 150 days after cortical ablation. A psychotomimetic cyelohexamine (1-(phenyl cyclohexyl) piperidine monohydrochloride, Sernyl) in doses of 4mg/Kg IP was tested, in view of previous evidence of effects on impedance in cerebral tissue (1). The same animals have been used in studies of the effects of ethyl alcohol on impedance, and results reported elsewhere (26).

Results

A. Impedance responses accompanying behavioral performances

Evidence for the progressive appearance of an "evoked" change in impedance in hippocampal tissue during acquisition of a visual discriminative habit has been presented elsewhere (2). The present study has considered effects of cue reversal on the daily computed average of hippocampal impedance during alerting, orienting and discriminative performances. A second phase of the study has concerned the variance between daily averages at different levels of training, in hippocampus, midbrain reticular formation and amygdala.

1. Daily averages of hippocampal impedance in approach training and cue reversal

At high performance levels, a sharp fall in hippocampal impedance occurred during the discriminative performance (Fig. 1). In this and the following figures, each 8 second analysis epoch has been marked with three

vertical bars, corresponding to the moments of successive presentations of the alerting tone stimulus, and the orienting (light on) and discriminative situations (door open). The major deflection accompanying the discriminative performance in this trained animal (Fig. 1A) occurred in the "capacitive" (reactive) lead. The daily averages varied in contour and magnitude of response, but typically an initial small fall in capacitance was followed by a larger rise. Return to baseline was followed by an overshoot lasting 3 to 5 seconds. The response began at, or slightly before, the time of door opening, and extended beyond the end of the animal's approach to food, which averaged about 1.5 seconds. The magnitude of this deflection was from 5 to 8 per cent of baseline impedance.

When behavioral cues were reversed, requiring an approach to the unlit side of the box for food reward, the impedance response sharply increased on the first day of training by comparison with days immediately preceding the reversal, (Fig. 1B). Thereafter, the daily averages showed a rapid decline and disappearance of the response. Exaggeration of the response on the first day after reversal is of interest in the light of a concurrent exaltation of regularity in averaged hippocampal EEG records under the same conditions (3).

With further retraining, the daily averageagain showed a small deflection during discrimination as performance rose above chance levels. Emergence of this deflection in the average was not related to latency of response, which had stabilized before attainment of the 50 per cent performance level. It will be noted that with retraining, the evoked response moved progressively to an earlier position, so that the initial inflection occurred slightly before opening of the doors. These findings suggest establishment of a time-trace conditioned reflex, of a type noted

previously in analysis of EEG records from the hippocampus (3), and is difficult to avoid in this test situation with necessarily fixed inter-stimulus intervals. Hippocampal impedance records failed to disclose any major deflections in relation to the alerting tone or presentation of the orienting situation, by contrast with the large and consistent response in discriminative performances in the trained animal, persisting into considerable degrees of overtraining.

Examination of similar computed daily averages for the amygdala and rostral midbrain reticular formation did not permit such clear interpretation. Responses were present in the midbrain reticular formation in both orienting and discriminative epochs, but waxed and waned over periods of several days, and were smaller than in the hippocampus. In the amygdala, consistent responses were not seen in these daily averages in any of the three epochs. For this reason, a more sensitive evaluation was sought, by computation of averages over periods of 5 successive training days. This calculation also allowed assessment of variance between daily averages over this period.

2. Impedance responses in hippocampus, amygdala and reticular formation during alerting, orienting and discrimination.

Calculation of 5-day averages for each of these structures in the course of training revealed patterns not detected in daily averages. Although "smearing" of responses not tightly time-locked to the cues was greater with this technique, the resultant smoothing enhanced more strictly related deflections.

a. Hippocampal responses

At high performance levels, 5-day averages of hippocampal impedance showed a large biphasic response during discrimination

with a sharp fall lasting about 1.5 seconds, followed by a slower rise above baseline (Fig. 2A). In this and subsequent figures, each plot shows three curves. The middle curve depicts the mean, the one above it indicates an upper limit of variability, since it shows the mean plus one standard error of the mean; and the lowest curve similarly describes the lower limit of variability. A smaller evoked decrease occurred on presentation of the alerting tone, with recovery of baseline impedance prior to commencement of discrimination. At 100 per cent performance level, variability was small throughout the analysis, increasing transiently in the reactive lead with presentation of the alerting tone.

A five-day average immediately after cue reversal was strikingly different (Fig. 2B). Variability widened sharply throughout the analysis epoch in both reactive and resistive leads. The large decrease in impedance during discrimination was reduced to one-fourth of its previous amplitude, and the response during alerting and orienting epochs was no longer discernible. In the course of retraining to the dark cue (Fig. 2C), variability again diminished to levels similar to those when fully trained in the light cue. At the 76 per cent performance level, the response during discrimination had increased to about half its amplitude at 100 per cent performance in the previous paradigm.

b. Midbrain reticular responses

Calculation of similar 5 day averages in midbrain impedance records also showed modifications of variability that related to levels of behavioral performance (Fig. 3).

These records, in a different subject from that in Fig. 2, showed a variability of the order of ± 2.5 percent of the mean capacitance, and ± 1.5 per cent of mean resistance at chance performance levels (Fig. 3A). When fully trained, variability had shrunk to narrow limits, and small responses were discernible during alerting and discriminative epochs (Fig. 3B). Immediately after cue reversal, variability again increased substantially, and evoked responses were no longer discernible (Fig. 3C). At this stage, the animal was perseverating in the use of the previous light cue, but with retraining to chance performance levels, impedance variability declined (Fig. 3D) and at 86 per cent performance was at a low level similar to that in Fig. 3B, at full training in the initial paradigm. In the retrained subject, small evoked responses occurred during the orienting epoch, rather than during alerting or discrimination.

c. Amygdaloid responses

Despite physical proximity to the hippocampus, and aspects of a common blood supply, evoked impedance changes in the amygdala (Fig. 4) of the same animal as in Fig. 2 bore no resemblance to the hippocampal responses. In light of the physiological role of the amygdala in long term states of alertness, relating to such functions as hunger, rage and sexual goals, it may be noted that, although variability declined progressively from chance performance

to full training (Fig. 4 A and B), the lowest variability occurred immediately after cue reversal (Fig. 4C), in contrast to the findings in the hippocampus and midbrain reticular formation. At this time, a small biphasic response occurred in the reactive lead, and a transient response late in discrimination was associated in most trials with completion of an incorrect approach.

Subsequent retraining with the dark cue to chance levels of performance (Fig. 4D) was still associated with a small response in the alerting epoch, now more obvious in the resistive than the capacitive lead, but there was no longer a clear response during discrimination.

It would thus appear that, whereas the largest and most consistent hippocampal responses were associated with discriminative performances, and in midbrain reticular formation with orientation and discrimination, the amygdala exhibited responses throughout training only in the alerting epoch. This regional specificity will be discussed further below.

B. Impedance phenomena during and following retrograde neuronal degeneration.

In further evaluation of the nature of these impedance responses, we have examined the role of neuronal elements, embedded in extracellular fluid and substantially surrounded by neuroglial cells, since, despite the high resistance path offered by neuronal membranes, neuronal activity may modulate conductance in surrounding tissue compartments.

1. Effects of visual cortical resection on baseline impedance in lateral geniculate nucleus.

Daily measurements of baseline impedance levels in the lateral geniculate nuclei were made for a minimum period of two months after bilateral electrode implantation. Typically in this period, there was a gradual decrease in variability in daily measurements (Fig. 5, upper and lower left).

Resection of the right visual cortex 50 days after implantation was followed by a reaction in geniculate impedance, beginning about seven days after operation. In the right lateral geniculate body, there was a sharp increase in resistance and capacitance, amounting to 30 to 50 per cent of baseline values (Fig. 5, lower right). These changes lasted about 10 days in the anterior electrode in the right lateral geniculate body, but persisted for about 30 days in the posterior lead, located in the main cellular laminae of the geniculate nucleus, and the site of the main degenerative phenomena. Here, the resistive lead showed a series of cyclic fluctuations with a periodicity of about 10 days, and largest in the third and last peak, with a doubling of resistance over baseline values. After an initial rise, capacitive readings in this lead showed a series of troughs which essentially mirrored simultaneous peaks in resistive values. After 30 days, resistive and capacitive readings resumed values similar to those seen preoperatively.

In the left lateral geniculate body, on the side opposite to the visual cortical resection, transient changes also occurred postoperatively (Fig. 5, upper right). A transient rise in resistance and capacitance occurred one week postoperatively, but no further perturbations were observed. Histological examination has not disclosed significant

degeneration here, in contrast to findings in the right lateral geniculate body.

2. Impedance phenomena in normal and degenerated geniculate tissue under the influence of 1-(phenyl cyclohexyl) piperidine monohydrochloride (Sernyl).

The role of nueronal elements in the multi-compartmental arrangement of cerebral tissue requires consideration of their interrelations with enveloping neuroglial and extracellular tissue. If they exercise some modulating influence on structures in their environment, then their removal would be followed by loss of such effects. With impedance measurements, such a sequence of events might be clearly disclosed, by reason of the preponderance of current flow through extraneuronal compartments, as discussed below. Manipulation of normal and degenerated geniculate nuclei with a cyclohexamine drug, Sernyl, indicated that such differential effects can indeed be detected.

Cyclohexamine drugs of this series have been extensively evaluated clinically in relation to induction of amnesic states and concomitant psychotomimetic effects. They are without significant effects on blood pressure or respiration (25), so that their effects on cerebral impedance appear to relate to direct influences on cerebral tissue (1, 35). Sernyl was administered 3 to 6 months after ablation of the visual cortex.

Typically, Sernyl in doses of 2 to 4 mg/kg by intraperitoneal injection produced a fall of 8 to 10 per cent in resistance in posterior geniculate leads in cellular zones of the nucleus (Fig. 6, LLG POST, posterior left lateral geniculate). A smaller fall in resistance occurred in anterior geniculate leads (Fig. 6, LLG ANT). These changes lasted about 90 minutes, with approximate return to baseline. Simultaneous

reactive measurements in the left nucleus showed comparable increases in capacitance. In striking contrast, resistive changes in the degenerated right geniculate nucleus were only about 2 per cent in its posterior zones (Fig. 6, RLG POST), now deprived of about 80 per cent of their neuronal population, and of the order of 1.0 per cent in anterior zones (Fig. 6, RLG ANT). Capacitive levels were not changed appreciably in the right posterior lead, and in the anterior lead, it appeared that a higher base-line was slowly established over a period of 100 minutes after drug injection.

These findings support the view that removal of the majority of neurons from a cerebral nucleus greatly diminishes impedance responses of pharmacological manipulations, in agreement with previous findings of diminished responsiveness to alcohol (26) in the cat, and decreased effects of hypocapnea in sclerotic human hippocampal tissue (34).

Discussion

This study has indicated that impedance of small volumes of cerebral tissue changed differentially at different sites in the course of a repertoire of alerting and learned responses. Moreover, the magnitude of these responses increased as levels of performance rose progressively above chance. They were susceptible to cue reversal and subsequent retraining. Variability, as indicated by standard error of the mean, in these impedance records was large in initial training trials, decreased progressively with training, reverted to wider levels on cue reversal, and decreased once more with retraining.

These impedance responses thus appear to relate to changes in intrinsic characteristics of cerebral tissue. Previous studies have

indicated that regional differences in impedance responses occur with shifts in carbon dioxide levels induced by hypercapnea or hyperventilation, both in man and animals, and that they do not arise in simple relationship to alterations in blood pressure, cerebral blood flow or brain temperature (4, 34).

Nevertheless, precise location of their site of origin in a tri-compartmental system comprising neurons, neuroglial cells and intercellular fluid has remained uncertain. From the Maxwell equations, as applied to conductivity of a solution with non-conducting bodies forming the dispersed phase, Cole (9) developed a cerebral model that took account of the high resistance of neuronal membranes, and concluded that a transneuronal pathway contributed insignificantly to conductance measured across the tissue as a whole. With a typical neuronal membrane resistance of the order of 1000 ohms/cm^2 (10), preferred current pathways would be anticipated through pericellular fluid, and perhaps through neuroglial cells. The contribution of neuroglial cells to the total conductance has been variously estimated. Hild and Tasaki (17) obtained values of 3 to 10 ohm/cm^2 in tissue culture. Kuffler and Potter (24) have reported much higher values in the giant neuroglial elements of leech ganglia, of the order of 1000 ohms/cm^2, and not substantially different from neuronal membrane resistance in the same preparation. These disparities may relate to differences in measuring technique, including control of carbon dioxide metabolism, to which attention has been drawn in studies in cells having neuroglial characteristics in the fish retina (37).

There is general agreement that extracellular space offers a high conductance pathway, but its precise relationship to the observed impedance requires consideration of the extent of the space in cerebral tissue, and

its content of macromolecular and ionic material. If it is the site of the impedance changes described here, then a substrate must be sought in a temporary and presumably reversible movement of ions into it, a movement presumably initiated in neuronal elements, but capable of modulation by neuroglial cells, or of influencing neuroglia, as discussed below.

Estimates of the extracellular space by electron microscopy have varied from as little as 4 per cent to as much as 24 per cent (15). These discrepancies may relate primarily to methods of fixation. Rapid neuroglial swelling with imbibition of fluid after death may lead to abnormally low figures, as may also the presence of certain cations in the fixative, as discussed below. Glutaraldehyde fixation (30) has yielded results closer to the cryogenic techniques of van Harreveld et al. than was possible with older osmic acid fixation. Estimates by chemical analysis have disclosed an extracellular space of approximately 15 per cent (36).

Movement of ions in the extracellular space will be substantially modified by the presence therein of macromolecules exhibiting ion-binding and fixed charge characteristics (23, 39), so that it is not possible to model ionic behavior in the perineuronal environment from consideration of a mere aqueous solution permitting unimpeded flow. The present study requires consideration of such macromolecules in terms of dynamic interactions with cellular elements that they surround, and their role in concurrent impedance phenomena.

Our findings of evoked impedance changes paralleling the level of learning suggest that changed conductance arises in the perineuronal environment, involving either neuroglial elements or intercellular fluid, or both. Green, Maxwell and Petsche (14) pointed out that the afterpotentials

accompanying repetitive hippocampal stimulation could be interpreted on the basis of extracellular ionic accumulation, perhaps involving potassium. In our studies, these impedance changes occurred facultatively in the course of learned responses, without major shifts in baseline impedance over the many days of training.

If these impedance changes occur in the narrow clefts between neuronal membranes and adjacent neuronal and neuroglial elements, conductance characteristics here will depend on their macromolecular content, as noted above. Identification of macromolecular material in electron micrographs of kidney and intestinal tissue led to a search for comparable intercellular substances in central nervous tissue (33). In sections of material prepared in ethylene and propylene glycol, and in the absence of calcium salts, Pease has disclosed substantial amounts of material in intercellular clefts in cerebral cortex, not revealed in classical electron micrographs prepared from fixed material. This substance stains strongly with phosphotungstic acid at pH3.5, thus differing from typical mucopolysaccharides, and its chemical identity remains undisclosed.

Katchalsky (23) has emphasized the susceptibility of such macromolecular polycarboxylic acids to precipitation by alkaline earth cations. Remarkable shrinkage in volume is induced by exchanging part of the sodium counter-ions at the membrane surface for calcium ions. Neurons in tissue culture, and dissected fragments of neuronal membrane, both exhibit electrokinetic effects in the presence of a focal E.M.F. in ways indicative of fixed negative membrane charges, and apparently related to adherent macromolecular layers (11, 12). In studies to be reported in detail elsewhere, as little as 40 microequivalents of intraventricular calcium solution was

found to change impedance of structures adjoining the ventricle by as much as 25 per cent for several hours (27).

We have so far considered ionic factors which might contribute to these impedance changes, either by their appearance in the intercellular fluid in the course of neuronal activity, as in the case of potassium, or by their ability to modify fixed charge characteristics of surface macromolecules, and thus, perhaps also, membrane permeability. Bennett (7) has termed these macromolecular envelopes "glycocalyces," and has suggested for them a direct role in determining differential entry of sodium and potassium to positions close to the plasma membrane. Others have proposed a role restricted to pinocytotic transfer of vesicular material, and specifically excluding a role in ionic mechanisms (8). Our findings suggest that impedance responses are mediated through perineuronal compartments; if we consider the two alternative paths through neuroglia or intercellular fluid, aspects of plastic responsiveness seen here may well have origins atrributable to an intercellular fluid characterized by a matrix of macromolecules.

Nevertheless, assignment of such a role exclusively to an interface between neuronal elements and a series of glycocalyces may substantially oversimplify interchanges to which the neuroglial compartment may also contribute (31), either by direct changes in neuroglial membrane resistance, or by modulation of conductance in intercellular fluid. Nicholls and Kuffler (30) have evaluated the intercellular fluid in leech ganglia as adequate in volume to subserve such a function, without significant neuroglial contribution to extraneuronal current flow. On the one hand, our results indicate that degenerative removal of the majority of neurons

from subcortical nuclei abolishes impedance responses to drugs effective in normal tissue, extending observations made by MacGillivray, Kado and Adey (26) with alcohol. Evidence from quite different sources continues to suggest a mutual interdependence of neurons and neuroglia in metabolic processes (18). Within the inevitable constraints of the Hyden technique, Hertz (16) has found evidence of increased metabolic activity in isolated neuroglial cells exposed to increased potassium ion concentrations, and no comparable effects in neurons. Location of enzymes by cytochemical techniques at neuronal-neuroglial and glial-glial interfaces (6) indicates that, if significant metabolic transactions occur in this way, they do so across a space in which the macromolecules may play a role, not only in modulation of ionic flow, but in the coding of chemical signals that would underlie long lasting changes in chemical structure of neuroglial cells interfacing with neuronal elements. Evidence of augmented neuroglial cell concentrations in brains of animals exposed to exalted sensory inputs has been offered by Altman (5), but pertains to white matter, rather than to cortical or nuclear structures. Nevertheless, the implication seems clear that attention should be directed specifically to the role of neuroglia in a micrometabolic module of neurons, neuroglia and intercellular fluid, insofar as this may determine substrates of information storage.

Footnote

(1) It is a pleasure to acknowledge the assistance of the National Institutes of Health through Grant MH-03708, and of the U. S. Air Force Office of Scientific Research through Contract AF(49)638-1387. Computations were supported in part by Contract NsG505 with the National Aeronautics and Space Administration. Histological sections were prepared by Miss C. Rucker and Miss A. Koithan. The figures were prepared by Miss H. Kowta.

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Legends to Figures

Fig. 1. Computed averages of hippocampal impedance records, each from 30 daily trials, at high performance levels (A), and after cue reversal with retraining (B). Left column, "reactive" readings; right column, simultaneous "resistive" readings (see text). In each column, first vertical bar marks onset of alerting tone, second marks presentation of cue light (orienting stimulus) and third, opening of start box doors. Response during discriminative epoch in reactive component (A) was exaggerated on first day after cue reversal (3/24/64), and disappeared immediately thereafter, but reappeared with retraining (B). Downward deflections in capacitance lead indicate increased capacitance (decreased impedance). Upward deflections in resistive lead show increase.

Fig. 2. Calculations of means and variability in hippocampal impedance over 5-day periods at various levels of training, in same animal as in Fig. 1. In each graph, the middle trace indicates the mean, with upper and lower traces showing one standard deviation from the mean. Calibrations indicate 50 picofarads, with mean baseline at 11.1 kilopicofarads throughout the training maneuvers; and 100 ohms, against a mean baseline of 16.0 Kilohms for the same period. Variability was low at 100 per cent performance (A), increased substantially immediately after cue reversal (B), but decreased again after retraining (C).

Fig. 3. Calculations of means and variability in midbrain reticular impedance in 5-day averages during initial training (A and B), immediately after cue reversal (C), and in retraining (D and E), with 3 traces in each graph, as in Fig. 2. Mean baseline was 4·2 Kilopicofarads for reactive lead, and 25 Kilohms for resistive lead. Calibrations: 50 picofarads, increasing with downward deflection; and 100 ohms, increasing with upward deflection. Changes in variability and in impedance responses are discussed in text.

Fig. 4. Calculations of means and variability in amygdaloid impedance in 5-day averages during initial training (A and B), immediately after cue reversal (C), and after retraining to chance performance levels (D), from same animal as in Figs. 1 and 2. Mean baseline was 6.5 kilopicofarads for reactive lead, and 18.5 Kilohms in resistive lead. Calibrations: 50 picofarads, increasing with downward deflection; and 100 ohms, increasing with upward deflection. Changes in variability and in impedance responses are discussed in text.

Fig. 5. Impedance measurements in anterior and posterior zones of both geniculate bodies from tenth day after electrode implantation until right visual cortical resection (February 10 to April 2), and following cortical resection (April 2 to May 22). Right posterior geniculate lead showed increasing impedance perturbations from 6 to 30 days postoperatively, and a brief disturbance also occurred in left geniculate leads at the sixth day (see text).

Fig. 6. Effects of cyclohexamine drug Sernyl (4 mg/Kg) on impedance of normal (left, LLG) and degenerated (right, RLG) lateral geniculate tissue. Drug induced large shift in posterior, cellular zones of normal left lateral geniculate, and less in anterior regions. Only small changes in capacitance or resistance occurred in degenerated right nucleus (see text). Figures at commencement of each tracing show baseline values in Kilopicofarads and Kilohms for each lead.